EDITORIAL

Anticoagulation in ischaemic heart disease

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Although treatments with oral anti-vitamin K agents have become more refined and safer over the years, physicians are reluctant to prescribe these agents for fear they will cause bleeding, particular in patients with ischaemic heart disease

Oral anti-vitamin K agents (AVKs) are the most frequently prescribed anticoagulants, and the fourth most prescribed cardiovascular agents. Even though four decades have passed since AVKs were first used to prevent thromboembolic disease, studies continue to discover and refine techniques that make treatment with this agent safer and more effective. In general clinical practice, physicians are often reluctant to prescribe AVKs, in part because they are not familiar with techniques for administering the drugs safely and fear that AVKs will cause bleeding. Patients treated with AVKs do require close monitoring to avoid bleeding, but it has been shown that these drugs prevent about 20 strokes for every bleeding episode that they cause. AVKs are mostly used for prevention of thromboembolic disorders in clinical settings such as atrial fibrillation, previous deep venous thrombosis (DVT)/pulmonary embolism (PE), and implantation of mechanical heart prostheses. Although AVKs are widely used in these conditions, the incidence and therapeutic management of ischaemic heart disease in patients receiving anticoagulant treatment need to be investigated further.

ORAL ANTICOAGULATION AND ISCHAEMIC HEART DISEASE: A DISPUTED LOVE

Thrombolysis is the mainstay in the antithrombotic treatment of patients admitted to hospital with acute myocardial infarction (AMI) with elevation of ST segment (STEMI) who are not candidates for PCI. Several fibrinolytic agents with different pharmacodynamic and pharmacokinetic profiles are routinely used.[1–2] Among patients with STEMI treated with thrombolysis, a significant proportion comprises subjects already under AVK treatment for previous acute coronary syndrome (ACS)/AMI or other conditions where the use of AVKs is mandatory, such as atrial fibrillation, heart failure, implantation of mechanical heart prostheses, or DVT/PE. However, the combination of anticoagulant and thrombolytic agents may theoretically cause severe haemorrhage. This possibility led the American Heart Association and the British National Formulary to propose a relative contraindication to thrombolysis in patients being treated with AVKs. However, from a clinical standpoint, the dilemma of whether or not to treat this class of patients with fibrinolytic therapy is still unresolved and clinicians still wonder about the best way to inhibit clotting or lyse thrombotic lesions in these patients, without enhancing their haemorrhagic risk.

THE PARADOX OF AMI OCCURRENCE IN ANTICOAGULATED PATIENTS

One limiting factor for the clinician attempting to determine the best way to treat this class of patient is the lack of extensive knowledge of their baseline risk profile. In this issue of *Heart* Oudot and colleagues[3] address the questions concerning the risk profile and in-hospital outcomes of patients on AVKs admitted to hospital for STEMI. In this observational study, which is part of a regional French survey (RICO) on the management of AMI, 2112 patients admitted for elevation of the ST segment were evaluated in regard to the impact of AVKs on therapeutic management and clinical outcomes. Two findings have to be particularly outlined in this study: (1) a significant number of patients were already receiving AVKs at the time of STEMI onset (4%); (2) the baseline risk profile of those patients being treated with AVKs was higher than that of the patients off AVKs, and was associated with more numerous adverse in-hospital outcomes.

If we take into account the rate of AMI in western Europe or the United States (approximately 1.5 million/year), and assume a similar proportion of patients already on AVKs at the moment of AMI occurrence, the number of subjects is not small and could exceed 50 000/year. These subjects might have worse outcomes and experience a higher rate of in-hospital complications, with enormous clinical and socioeconomic costs. Moreover, these patients received less frequently antiplatelet (aspirin and thienopyridines) drugs and heparin treatment in the acute phase, although, unexpectedly, the rate of administration of glycoprotein IIb/IIIa antagonists was similar in the two groups (about 30%). Altogether, these observations raise a series of intriguing questions. Would the anticoagulated patients have benefited more from prior antiplatelet and AVK therapy, based on a more accurately determined risk profile? Why were their in-hospital clinical outcomes worse,

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Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; AVKs, anti-vitamin K agents; DVT, deep vein thrombosis; CGIH, gastrointestinal haemorrhage; ICH, intracranial haemorrhage; PCI, percutaneous coronary intervention; PE, pulmonary embolism; STEMI, ST segment elevation myocardial infarction

particularly in regard to the occurrence of heart failure?

While a higher incidence of bleeding complications in the AVKs patients was predictable, it was rather unexpected that in multivariate analysis AVKs were an independent risk factor for in-hospital heart failure. Because of the small number of observations, Oudot and colleagues[3] do not provide any evidence of co-morbidity as potential causes of heart failure. Although the detailed nature of linked co-morbidity is unknown, this hypothesis seems reasonable. However, the finding that the baseline risk profile was higher in the AVK patients may be the consequence of the routine clinical habit of administering AVKs long term, rather than antiplatelet drugs—a practice prevalent in the treatment of cardiovascular patients in more severe clinical circumstances where the risk of haemorrhagic complications needs to be adequately counterbalanced by a strong reduction in the thrombotic risk. This occurs especially in older patients with prior AMI, stroke, or diabetes—all conditions that in this study had a higher incidence in the AVK group.[3] In this clinical setting, the patients should be treated, when possible, with combination therapy based on antiplatelet and AVK drugs (target international normalised ratio (INR) 2.5, range 2.0–3.0), according to a grade 2B recommendation of the evidence based guidelines of the American College of Chest Physicians.[4] We could thus speculate that with combination therapy the risk profile of these patients would have been reduced.

IS THROMBOLYSIS CONTRAINDICATED IN STEMI PATIENTS RECEIVING AVK?

Another intriguing study presented in this issue of *Heart* is that by Stanley and colleagues,[5] which addresses the question of whether or not thrombolysis is contraindicated in the class of patients receiving AVKs admitted to the hospital for STEMI. This study, in a large cohort of patients (2437) with STEMI, shows that in 50 of them receiving AVKs, thrombolysis did not enhance significantly the cumulative incidence of severe bleeding episodes, such as intracranial (ICH) or gastrointestinal (GIH) haemorrhage (8% *v* 6.3%, p = NS). However, the authors also showed in a small number of patients receiving AVKs that age and blood pressure were significant risk factors for severe haemorrhage after thrombolysis. This result is in agreement with findings of a recent observational study showing that the incidence of bleeding events increases exponentially in patients > 80 years of age being treated with AVKs.[6] Although the small number of observations does not allow for definitive advice to be forthcoming in this field, the study suggests that thrombolysis could not be avoided in patients < 75 years old with INR values < 3.0 on admission. This study paves the way for a randomised multicentre study to address this intriguing issue.

CONCLUSIONS AND FUTURE DIRECTIONS

Globally the results of the two studies reported in this issue of *Heart* provide useful though not definitive indications for the acute management of anticoagulated patients with STEMI.[3 5] In particular, these results draw attention to the need to collect more extensive data on the baseline risk profile of those patients who are candidates for AVK therapy alone or in combination with antiplatelet agents, especially in regard to the risk of heart failure. This approach is needed to optimise the use of AVKs in cardiovascular patients, whose thrombotic and haemorrhagic risk should be carefully estimated.

In subjects aged > 75 years and systolic blood pressure > 150 mm Hg being treated with AVKs, the use of thrombolysis should be avoided. Likewise, inferring from the dataset on the ''non-warfarin'' group in the study by Stanley *et al*,[5] thrombolysis should be avoided to minimise the risk of ICH or GIH in subjects with STEMI receiving AVK therapy in combination with antiplatelet agents. Conversely, in patients aged < 75 years with systolic blood pressure < 150 mm Hg, the use of thrombolytic agents is not contraindicated in warfarin-treated patients, although more data are needed to address this issue with more confidence.

While we are waiting for future randomised controlled trials on clinical outcomes of patients treated with new anticoagulants, such as direct thrombin inhibitors and activated factor X inhibitors,[7] further trials are currently needed to tailor our efforts to optimise the risk/benefit profile of AVK-based therapy in the individual patient. Only this strategy will enable us to determine the acceptable risk associated with thrombolytic treatment.

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